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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/237,291	01/25/99	YOUNG J	SYS-2068

001095 HM12/1027
MELVYN M KASSENOFF
NOVARTIS CORPORATION
PATENT AND TRADEMARK DEPT
564 MORRIS AVENUE
SUMMIT NJ 07901-1027

EXAMINER	
SCHMIDT,M	
ART UNIT	**PAPER NUMBER**
1635	6

DATE MAILED: 10/27/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/237,291	Applicant(s) Young et al.
	Examiner Schmidt	Group Art Unit 1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on August 11, 1999 (Paper 4).

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 18-20, 24-98 and 91-47 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 18-20 24-27, 31-44 and 46-47 is/are rejected.

☒ Claim(s) 28 and 45 is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☒ Notice of References Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

DETAILED ACTION

1. Acknowledgment is made to cancel claims 1-17, 21, 22, 29 and 30, amend claims 18-20, 23-27 and add claims 31-47.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-20, 23-27, 31, 37-44 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al. (US Patent 5,665,557) , Nakahata (US Patent 5,861,315), Hoffman et al. (US Patent 5,744,361), Fei et al. (US Patent 5,635,387) or Davis et al. (US Patent 5,599,703), in view of Ku et al, Kobayashi et al, Ramsfjell et al (IDS Reference AK), Ohmizono

et al, Szilvassy et al, Escary et al., or Bodine et al, and further in view of Tushinski et al (IDS Reference AN), Fletcher et al., Bello-Fernandez et al, or Hatzfeld et al.

The claims are drawn to methods of culturing human hematopoietic stem cells in media comprising mpl ligand, flt3 ligand (FL), c-kit ligand, IL3, TPO, IL6 and/or LIF, and further, genetically modifying said cells via contacting a retroviral, adenoviral or adeno-associated viral vector with the hematopoietic stem cells in culture. Specifically, the claims are drawn to the following concentrations of growth factors (1) 0.1- about 500 ng/ml *mpl ligand* and *flt3 ligand* (claim 18), further, with 5- about 200ng/ml *c-kit ligand* (claim 19), and further, with 5- about 200 ng/ml *IL3* (claim 20); (2) 0.1- about 500 ng/ml *TPO*, *flt3 ligand* and *IL6* (claim 23 or claim 37), further with (a) 5- about 200 ng/ml of *LIF* (claim 24 or claim 39), or (b) 10 - about 100 ng/mL of *IL3* (claim 25 or claim 40), and further with 5- about 200 ng/mL of *c-kit ligand* (claim 27), or c) 5- about 200ng/mL of *c-kit ligand* (claim 26); (3) 5- about 200 ng/mL *TPO* and *FL* each, and about 10- about 100 ng/mL *IL6* (claim 31). The claims further specify the hematopoietic cells as CD34+Thy-1+ Lin- cells and the heterologous gene as a marker gene or a therapeutic gene.

Murray et al. (US Patent 5,665,557), Nakahata (US Patent 5,861,315), Hoffman et al. (US Patent 5,744,361), Fei et al. (US Patent 5,635,387) and Davis et al. (US Patent 5,599,703) are all relied upon to teach methods of isolating and culturing populations of human hematopoeitic stem cells. They do not necessarily teach the combinations of cytokines taught in the instant specification for growth of the stem cells in culture nor do they necessarily teach retroviral mediated gene transfer into the isolated and cultured populations of hematopoietic stem

cells. Specifically they teach for instance: (1) 10ng/ml IL-3, 2ng/mL GM-CSF, 100ng/mL SF and 2 units/mL of EPO (Murray et al., col. 5-6 and col. 16, lines 20-22); (2) 50ng/mL IL-6 and/or 100ng/mL SCF (Nakahata, col. 6, line 38); (3) 10-500ng/mL c-kit ligand (MCF) and at least one of IL-3 (.5-2ng/mL), GM-CSF (.1-1 ng/mL), IL-1 (I-10 U/mL), or IL-6 (.5-10 ng/mL) (Hoffman et al., col 4, lines 50-60); (4) 50 ng/mL SGF, 50 ng/mL IL#, 20 ng/mL GC-SF (Fei et al., col 18, lines 65-67 and col. 19, lines 1-23); and (5) 0.1-20 ng/mL GM-CSF, 1-200 ng/mL IL3, 5-500 ng/mL SCF and/or 1- 100 ng/mL IL6 (Davis et al., col 9, lines 11-32).

Ku et al., Kobayashi et al., Ramsfjell et al. and Ohmizono et al. are further relied upon to teach the effects of Tpo (mpl-ligand) and flt-ligand on human hematopoietic stem cells in culture. They do not necessarily teach retroviral mediated gene transfer in such cultured cell populations.

Szilvassy et al. and Escary et al. are further relied upon to teach the effects of LIF on hematopoietic stem cells in culture. They do not necessarily teach retroviral mediated gene transfer in such cultured cell populations.

Bodine et al. is further relied upon to teach the effects of SCF (c-kit ligand) and IL-6 on hematopoietic stem cells in culture. They do not necessarily teach retroviral mediated gene transfer in such cultured cell populations.

Tushinski et al., Fletcher et al., Bello-Fernandez et al. and Hatzfeld et al. are further relied upon to teach retroviral mediated transfer of genes into hematopoietic stem cells in culture. They do not necessarily teach the same culture condition instantly claimed.

It would have been prima facie obvious to one of ordinary skill in the art to culture human hematopoietic stem cells in mpl-ligand, flt3 ligand, c-kit-ligand, IL3, LIF, TPO, and/or IL6 since Murray et al. (US Patent 5,665,557), Nakahata (US Patent 5,861,315), Hoffman et al. (US Patent 5,744,361), Fei et al. (US Patent 5,635,387), Davis et al. (US Patent 5,599,703), Ku et al, Kobayashi et al, Ramsfjell et al, Ohmizono et al, Szilvassy et al, Escary et al., and Bodine et al. all teach methods for isolation and culturing of hematopoietic stem cells via addition of one or more of mpl-ligand, flt3 ligand, c-kit-ligand, IL3, LIF, TPO or IL6. It would have been further prima facie obvious to genetically modify said cultured cells via a retroviral vector since Tushinski et al., Fletcher et al., Bello-Fernandez et al. and Hatzfeld et al. all teach methods of retroviral mediated transfer into hematopoietic stem cells.

One of ordinary skill in the art would have been motivated to culture human hematopoietic stem cells via the methods taught by Murray et al. (US Patent 5,665,557), Nakahata (US Patent 5,861,315), Hoffman et al. (US Patent 5,744,361), Fei et al. (US Patent 5,635,387), Davis et al. (US Patent 5,599,703), Ku et al, Kobayashi et al, Ramsfjell et al, Ohmizono et al, Szilvassy et al, Escary et al., and Bodine et al. and further to transfect genes via retroviral vectors such as those taught by Tushinski et al., Fletcher et al., Bello-Fernandez et al. and Hatzfeld et al.

One of ordinary skill in the art would have had an expectation of success to culture hematopoeitic stem cells in mpl-ligand, flt3 ligand, c-kit-ligand, IL3, LIF, TPO, and/or IL6 for the effects taught by Murray et al. (US Patent 5,665,557), Nakahata (US Patent 5,861,315), Hoffman et al. (US Patent 5,744,361), Fei et al. (US Patent 5,635,387), Davis et al. (US Patent 5,599,703),

Ku et al, Kobayashi et al, Ramsfjell et al, Ohmizono et al, Szilvassy et al, Escary et al., and Bodine et al. One of ordinary skill in the art would have had an expectation of success to genetically modify such human hematopoietic stem cells in culture via retrovirally mediated gene transfer as taught by Tushinski et al., Fletcher et al., Bello-Fernandez et al. and Hatzfeld et al.

3. Claims 28 and 45 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

M. M. Schmidt
October 25, 1999

George C. Elliott, Ph.D.
Supervisory Patent Examiner
Technology Center 1600